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LETTERS AND CORRESPONDENCE

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Reactive Hemophagocytic Syndrome and Hodgkin's Disease

To the Editor: Reactive hemophagocytic syndrome (RHS) is characterised by the constellation of fever, hepatosplenomegaly, profound pancytopenia, impaired liver function, and proliferation of benign hemophagocytic histiocytes throughout the reticuloendothelial system. It was initially described in association with viral disease and distinguished from malignant histiocytosis [1]. Subsequently, it was found to be associated with bacterial, viral, and fungal infections, lymphoma (mostly peripheral T-cell lymphoma) [2,3] and autoimmune disease as systemic lupus erythematosus [4]. RHS complicating malignant lymphoma is usually associated with a poor prognosis and may present as the terminal phase of the disease after a variable period of stable disease [2]. Hodgkin's disease, however, has not been described to be associated with RHS.

A 17-year-old boy presented to us with a 1-month history of intermittent fever, night sweats, and weight loss of 30 lb in 4 months. Physical examination showed that the patient was febrile and pale and that he had a left cervical lymph node measuring 4 cm in diameter and hepatomegaly of 7 cm and splenomegaly of 5 cm. The complete blood picture showed hemoglobin (Hb) 8.9 g/dl, leukocyte count 1.46 × 10^9/L, and platelets 72 × 10^9/L. Serum biochemistry showed albumin 27 g/L, globulin 18 g/L, bilirubin 16 μmol/L, alkaline phosphatase 989 U/L, AST 536 U/L, ALT 257 U/L, LDH 1,435 U/L, and β2-microglobulin 8.2 μg/ml. Prothrombin time (PT) was 14 sec, activated partial thromboplastin time (aPTT) 42 sec, INR 1.2, fibrinogen degradation product (FDP) <10 mg/L, and fibrinogen level normal. Direct Coomb's test was negative. Blood, sputum, and urine cultures were negative. Bone marrow aspirate revealed normocellular marrow, normal hematopoiesis, prominent hemophagocytic histiocytes (accounting for 5% of all nucleated marrow cells), infiltration large lymphoma cells with prominent nucleolus (Fig. 1), and the presence of occasional Reed-Sternberg cells. Trephine biopsy showed focal Hodgkin's disease, normal hemopoiesis and no marrow fibrosis. Lymph node biopsy showed an abnormal cellular infiltrate in the paracortex consisting of Reed-Sternberg cells and Hodgkin's cells in a background of lymphocytes and histiocytes, compatible with Hodgkin's disease, mixed cellularity. Computed tomography (CT) of the abdomen revealed hepatosplenomegaly, but no paraaortic lymph nodes. The patient was stage IVB by Ann Arbor staging. COPP-ABV hybrid (D1, cyclophosphamide 450 mg/m^2, vincristine 1.4 mg/m^2; D8, Adriamycin 35 mg/m^2, bleomycin 10 mg/m^2, and vinblastine 6 mg/m^2, procarbazine 100 mg/m^2 D1–7; prednisone 40 mg/m^2 D1–14) was started. The pancytopenia gradually improved after the first course of chemotherapy as shown. The patient attained complete remission and is disease free 17 months after treatment.

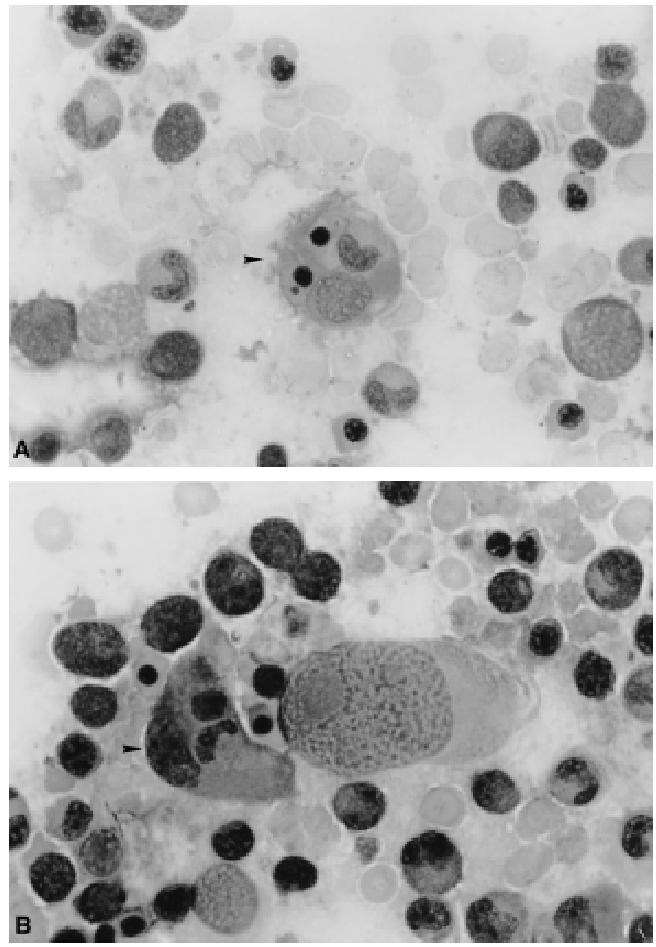

Fig. 1A & B. Hemophagocytic histiocytes (*arrow*) in the bone marrow aspirate (Giemsa, ×800). In panel B, the hemophagocytic histiocyte lies adjacent to a large mononuclear Hodgkin cell.

Our patient had a classic presentation of RHS with fever, hepatosplenomegaly, impaired liver function, and pancytopenia, and prominent hemophagocytic histiocytes (5% of all nucleated marrow cells). Previous reports of lymphoma associated RHS were mainly patients with peripheral T-cell lymphoma; the mechanism was thought to be the consequence of cytokines released by the lymphoma cells. Our patient presented with RHS at diag-

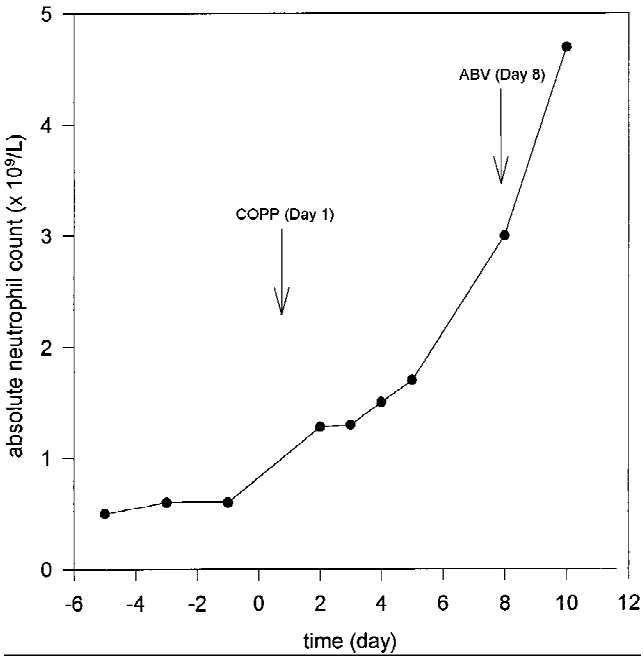

Fig. 2. Rise of leukocyte count without drop nor nadir during first induction with intensive chemotherapy.

nosis, in contrast to RHS associated with peripheral T-cell lymphoma, in which RHS may be a terminal event after a stable course for variable periods [2]. In previous studies of a total of 55 Hodgkin's disease patients with marrow involvement, prominent hemophagocytic histocytosis were not described [5,6].

Although our patient has stage IV Hodgkin's disease, its focal involvement could not explain the profound pancytopenia. Moreover, a previous study [5] of 36 marrow-positive Hodgkin's disease patients showed most to have normal blood counts. Moreover, in another study of Hodgkin's disease with marrow involvement [6], when combination chemotherapy (MOPP) was given to the patients with initial leukopenia, severe leukopenia occurred, with 42.8% developing life-threatening infections. In our patient, despite the severe initial neutropenia, the leukocyte count actually rose, instead of dropping, during the initial phase of induction chemotherapy (Fig. 2), and our patient tolerated the chemotherapy very well without complications. Although marrow-positive Hodgkin's disease with non-RHS leukopenia was reported to have a poor prognosis due to a low remission rate [6], our patient illustrated that RHS-associated leukopenia in Hodgkin's disease could respond favourably to chemotherapy.

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Low Levels of Plasma Stem-Cell Factor in a Patient With Cyclic Neutropenia

To the Editor: Cyclic neutropenia is a rare disorder occurring in children and adults. However, the pathogenetic mechanism is unknown [1]. The proposed mechanisms involve a defect in the production of hematopoietic stem cells, mainly in granulopoiesis, or immunological abnormality as evidenced by the excess of large granular lymphocytes and the response to immunosuppressive agents [1]. Although cycling is most prominent in neutrophils, fluctuations have been observed in all blood components [1]. Thus, there may be fundamental defects in hematopoiesis affecting the production of all lineages of hematopoietic stem cells, or in the function of the microenvironment of the bone-marrow stroma supporting hematopoiesis.

We previously reported fluctuation in plasma cytokine levels in a patient wtih cyclic neutropenia; the greatest fluctuation was found in G-CSF, and the TNF-α level fluctuated inversely with that of G-CSF, while oscillation of IL-6 preceded that at the G-CSF level [2].

The administration of growth factors such as G-CSF increased the peripheral blood neutrophil count but amplified oscillation, and GM-CSF also eliminated the multilineage oscillation of circulating blood elements [3].

It is known that c-kit is expressed on early hematopoietic progenitors, while stem-cell factor (SCF), which is a ligand for c-kit, is expressed only by stromal cells including endothelial cells and fibroblasts, and serves as a multipoietin which acts on early hematopoietic progenitors in synergy with other cytokines such as IL-3, IL-6, and G-CSF [4]. SCF also exists as a soluble form by means of proteolysis in the plasma [4]. We measured the plasma levels of SCF to determine the pathogenesis of cyclic neutropenia.

The patient was a 35-year-old female with cyclic neutropenia with a 21-day cycle, that had been diagnosed at age 10.

Blood was drawn and anticoagulated with EDTA. Plasma was separated immediately by centrifugation, and frozen at −80°C until assay. Levels of SCF were measured by the sandwich enzyme immunoassay technique, using a Quantikine human SCF immunoassay kit (R&D Systems, MN).

SCF levels were below normal range at all points of measurement (normal range (mean ± SD), 1,622 ± 314 pg/ml) (Fig. 1). However, those levels did not fluctuate significantly, with fluctuations in each element of leukocytes.

The significance of the low levels of SCF at all points of measurement during one cycle of neutropenia is not clear. In aplastic anemia and myelodysplastic syndrome, plasma levels of Epo and G-CSF were increased due to increased endogenous production in contrast to low levels of plasma SCF, suggesting abnormalities of cells within the microenvironment [5,6]. There may be a fundamental defect of hematopoiesis in the early stages of hematopoiesis in cyclic neutropenia as a defect of production of growth factor or as a defect in the function of microenvironment, as supposed in aplastic anemia. The feedback mechanism for the production of soluble SCF may be nonfunctional in cyclic neutropenia, as in aplastic anemia and myelodysplastic syndrome of bone-marrow failure [5,6]. The absence of significant fluctuation in the levels of SCF might indicate that small changes in SCF concentration could exert a major effect on hematopoiesis. However, the mechanism of cycling of blood elements still could not be explained in this context.

SCF primarily exists attached to stromal cells, which functions more significantly than the soluble form [4]. Further measurement of the m-RNA gene of SCF in bone-marrow stromal cells, and of their transcription prod-